

Validation of a Best-fit Pharmacokinetic Model for Scopolamine Disposition after Intranasal Administration

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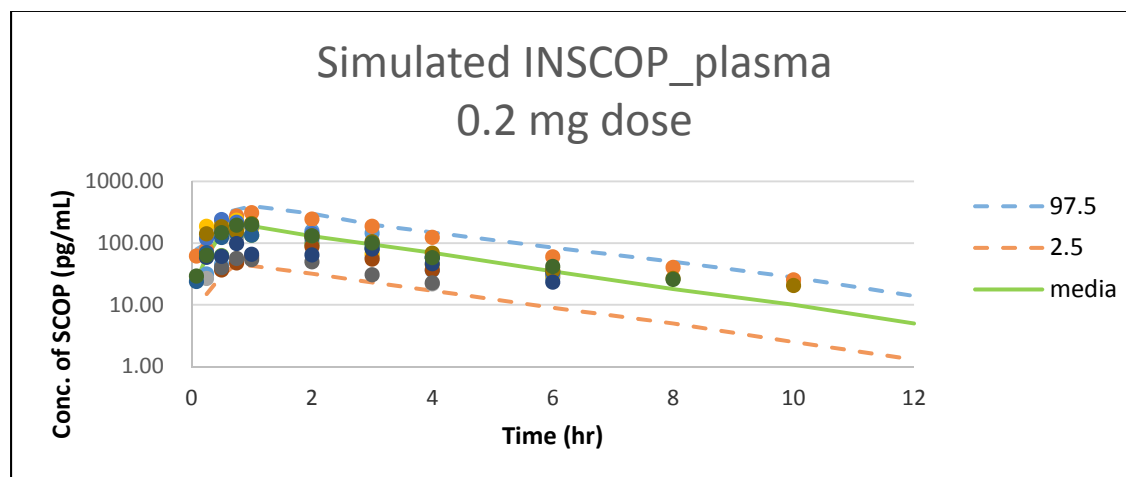
Introduction: An intranasal gel formulation of scopolamine (INSCOP) was developed for the treatment of Motion Sickness. Bioavailability and pharmacokinetics (PK) were determined per Investigative New Drug (IND) evaluation guidance by the Food and Drug Administration. Earlier, we reported the development of a PK model that can predict the relationship between plasma, saliva and urinary scopolamine (SCOP) concentrations using data collected from an IND clinical trial with INSCOP. This data analysis project is designed to validate the reported best fit PK model for SCOP by comparing observed and model predicted SCOP concentration-time profiles after administration of INSCOP.

Methods: For validation of reported PK model, we used data from the clinical trial in which twelve healthy human subjects were administered two dose levels (0.2 and 0.4 mg) of INSCOP. Concentrations of plasma, saliva and urine were measured by using a validated LC-MS-MS assay. Pharmacokinetic compartmental models, using actual dosing and sampling times, were built using Phoenix, by minimizing the Akaike Information Criteria (AIC) and by the comparison of the plots of quality. Simulation was performed using resampling option of Phoenix NLME. The 95% confidence interval for 500 runs of simulation was determined and the observed data were compared using 95% confidence interval (CI) for plasma profiles. Concentrations of SCOP in saliva were used to simulate plasma concentration-time profiles of SCOP. The percentage of difference between simulated and observed salivary concentrations at each time point was determined.

Results: The best fit PK model for INSCOP consisted of one compartment each for plasma, saliva and urine, with different rate constants of distribution among the three compartments. Simulated plasma concentration profiles after 0.2 and 0.4 mg dose of INSCOP administration were shown in Figure 1. Most of the observed values in plasma for 12 subjects from the 500 simulation runs were within the 95% CI. Comparison between predicted and observed plasma concentrations of SCOP as a function of time were presented in Table 1. The percentage of difference between simulated and observed concentrations was less than 40% before 6 hours post dose for 0.2 mg and up to 12 hours for 0.4 mg dose. SCOP plasma concentrations from observed and simulated profiles were comparable throughout the entire disposition profile of the drug after both doses of administration.

Conclusion: Validation of the best fit PK model developed by simultaneously fitting plasma, saliva and urinary excretion data for predicting systemic SCOP levels after INSCOP administration was achieved. The predictive power of the validated model is confirmed that saliva samples can be successfully used to predict plasma concentrations of SCOP after INSCOP administration. These results support application of non-invasive saliva sampling for the assessment of PK of SCOP.

(a)



(b)

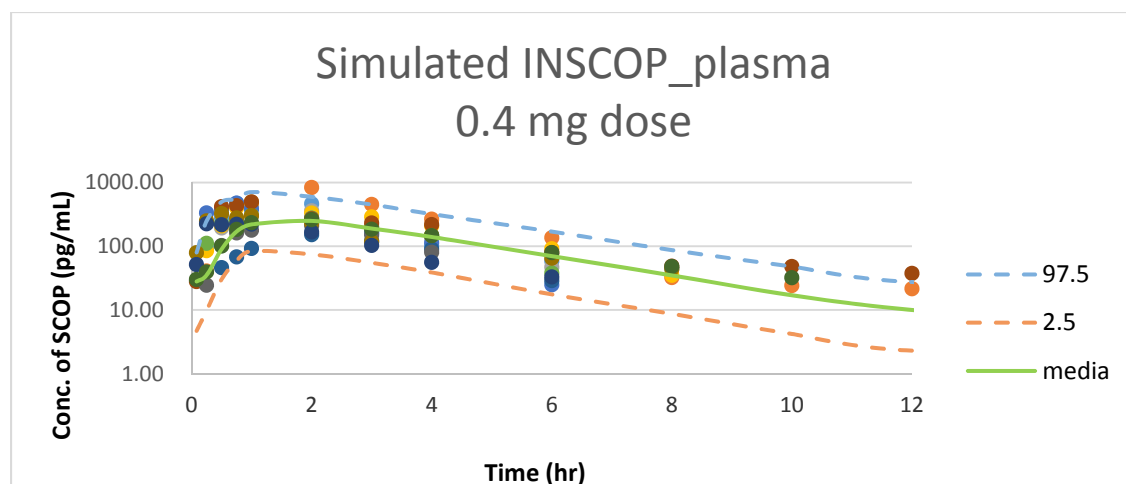


Figure 1. Simulated plasma concentration versus time profiles after 500 simulations post (a) 0.2 mg and (b) 0.4 mg doses of INSCOP administration. Each datum point represented observed concentration from 12 subjects. The solid line indicated 50th percentiles, and broken lines represented 2.5th and 97.5th percentiles from model estimations of 500 simulations.

(a)

Time (Hour)	Observed Conc.(pg/mL)	Simulated Conc.(pg/mL)	% of Difference
0.00	0.00	0.00	0.00
0.25	85.22	NA	NA
0.50	193.17	168.40	12.82
0.75	284.51	NA	NA
1.00	263.58	231.50	12.17
2.00	193.60	159.50	17.61
3.00	149.63	101.80	31.97
4.00	93.83	57.20	39.04
6.00	32.38	19.70	39.15
8.00	14.25	6.12	57.05
10.00	6.01	4.21	29.93
12.00	8.84	3.67	58.49
24.00	5.23	1.25	76.08

(b)

Time (Hour)	Observed Conc.(pg/mL)	Simulated Conc.(pg/mL)	% of Difference
0.00	0.00	0.00	0.00
0.25	231.90	NA	NA
0.50	383.40	321.04	16.26
0.75	540.18	NA	NA
1.00	522.01	462.12	11.47
2.00	447.56	404.38	9.65
3.00	277.50	210.81	24.03
4.00	175.46	109.57	37.55
6.00	77.83	57.21	26.49
8.00	38.38	24.89	35.15
10.00	17.63	13.87	21.34
12.00	3.83	2.58	32.70
24.00	2.69	1.37	49.10

Table 1. Comparison of model predicted using saliva data and observed values of SCOP in plasma as a function of time after administration of (a) 0.2 mg and (b) 0.4 mg dose of INSCOPs.